REMARKS

Claims 1-8, 12-14, 16, 18-22, 24-29, 38-56, 60, 61, 64, and 65 are subject to examination. Of these, claims 1, 8, 19, 51, 64 and 65 are independent.

The Applicant's remarks are prefaced by the Examiner's rejection in small bold-faced type.

Rejections for Indefiniteness

The Examiner stated:

> **Claim 1 recites a step of "sampling or evaluating " amino acids or rotamers "within the context" of a protein sequence (or sequences)and a backbone structure. Claim 19 recites a step of "evaluating" fitness of amino acids "within the context" of a protein sequence and structure. Claim 56 also recites "evaluating" fitness of rotamers "within the context" of a protein sequence and spatial constraint. It is unclear what is meant by "sampling" or "evaluating" amino acids or rotamers within "the context" of a protein sequence and structure or spatial constraint. Does applicant intend to take actual samples of amino acids or peptide structures (rotamers), or does applicant intends to do something (e. g. in silica steps) with amino acid or rotamer coordinates or other computer representations?**

The sampling and evaluating are typically effected by a computer and do not require evaluating a physical protein molecule.

> **Further, it is unclear what method steps or limitations are intends by "in the context" of a protein sequence and backbone structure or spatial constraint. Does applicant intend a comparison of some sort; e. g. an alignment, or identity or homology determination? Or does applicant intend a fitting or docking-type of calculation? Or does applicant intend a calculation of energy configurations or application of an algorithm in determining addition of amino acids or rotamers to a backbone to generate a protein structure? As it is unclear what steps and/or limitations are intended by the "sampling " or "evaluating " steps of claims 1 and 51, the claims are indefinite.**

Although the Applicant asserts that the term "context" is definite, to obviate the Examiner's concerns about the term and to expedite prosecution, the claims have been amended to remove this term. For example, in claim 1, the Applicants have indicated that the method includes sampling and evaluating fitness of one or more amino acids at positions in at least one

backbone structure. Sampling and evaluating can be performed using any appropriate method, including those embodied in the specification.

Claims 3, 26, 60 and 61 each recites a step of generating or producing a protein or library of proteins from a probability matrix. It is unclear if applicant intends to generate actual proteins (e. g. from a protein synthesizer), or intends to generate a list of protein sequences (i. e. a virtual library) identified or designed by the matrix of claims 1 and 19. Applicant is advised that a step of actually synthesizing proteins directly from a matrix is not supported or enabled by the instant specification; however, as applicant 's intended limitation is unclear, the claims are rejected herein only for indefiniteness. It is noted that claim 25, which clearly recites generation of a protein sequence, is definite.

Claims 3, 26, 60, and 61 refer to producing actual proteins. The Applicant defers responding to the Examiner's comment that the specification does not support these claims until an actual rejection is entered, except to note the high level of skill in the art of producing proteins and the teachings of the specification, e.g., at pages 6-7.

Claims 8, 18, 29, 51 recite limitations which "satisfy " a constraint or constraints. It is unclear what conditions must be met to "satisfy " a constraint; i.e. must some limit or threshold be met, or exceeded, or must an energy level be below a certain limit, etc.? As the metes and bounds intended by applicant by the term "satisfy " as applied to a constraint, are unclear, the claims are indefinite.

The term "satisfy a constraint" is a term of art. The condition that must be met is the "constraint." In one embodiment, a particular structural form (see, e.g., claim 52) can be used as a constraint. As the term is well known in the art and encompasses the various examples offered by the Examiner, the term is definite.

Claims 39-40 limit a library to be "designed by " various procedures. It is unclear what structural limitation of the library elements is intended by the "design " limitations. If applicant intends to limit the method of claim 26, and thereby parent claim 19, then it is unclear what method step is intended to be limited, or whether applicant intends further method steps. It is noted that parent claim 26 is directed to producing a library, and does not recite a design step. Claim 19, from which claim 26 depends, also fails to recite a design step. If applicant intends to limit the method of claim 19 or claim 26 to comprise further method steps, then applicant is advised to clearly indicate this intention and to recite any method steps using active, positive claim language.

Claims 39 and 40 have been amended to recite positive claim language.

Claim 44 limits the method of claim 1 to comprise freezing side chain identities and rotamers at "all other positions " in the protein. As no individual "position " or "positions " are identified in claim 1, it is unclear what "other positions " are

intended to be frozen in claim 44, therefore the claim is indefinite. For purposes of search, this claim is interpreted to recite that rotamers and/or side chains may be evaluated individually.

Claim 44 has been amended.

Claim 48 limits the method of claim 3 to further comprise screening or selecting one or more proteins from the generated combinatorial library. However, claim 48 does not recite any parameters for screening or selecting, such that one skilled in the art would be apprised of the metes and bounds intended by applicant for the protein to be thus chosen. As is it unclear what the protein in intended to be selected or screened for (or against), the claim is indefinite.

Methods for screening and selecting proteins from libraries are well known in the art. The claim is not limited by a particular parameter. As noted in MPEP § 2173.04, "breadth is not indefiniteness."

The terms "enhanced " and "improved " in claim 50 are relative terms which renders the claim indefinite. The term terms "enhanced " and "improved " are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the proteins are intended to be "enhanced " or "improved " relative to. In addition, it is not clear what is intended by an "enhanced " activity (e. g. a higher binding affinity may be considered "enhanced " for an compound which acts as a receptor agonist whereas a lower binding affinity would be considered "enhanced " for an antagonist). Nor is it clear what is intended for an "improved " stability (e. g. for a drug wherein a faster clearance rate is desired, a compound with a lower stability may be considered "improved"). For these reasons, the claim is indefinite.

Claim 50 has been amended to address the Examiner's concerns.

Rejection for Anticipation in view of Koehl (1994)

The Examiner asserted:

Claims 1, 4-8, 12-14, 18-21,27-29,41-47,49,51-56, and 64-65 are rejected under 35 U. S. C. 102(b)as being anticipated by KOEHL et al. (J. Molec. Biol. (1994) vol. 239, pp. 249-275).

KOEHL teaches a computerized method of generating a global conformational (probability) matrix representing a protein structure (p. 250) wherein an averaged rotamer (backbone)library or ensemble is provided (p. 251)a self consistent mean field theory/algorithm (SCFM)is used to generate possible side chain sequences and to evaluate all possible rotamers in "the context" of the backbones and side chain sequences to generate the matrix (pp. 251-252 and 256-257), thus anticipating claims 1,5, 19 and 44, and 65. KOEHL teaches that the protein and/or backbones may be derived from or based on comparison to a

natural protein (pp. 254-255), thus anticipating claims 6-7, 14, 20-21, and 27-28. KOEHL further teaches that her matrix calculations comprise information from partition functions (p. 254) and comprise information for all amino acids (p. 259, esp. Table 3), thereby anticipating claims 45 and 47. KOEHL teaches that his method steps may be iterated in multiple cycles, using multiple matrices, until convergence is reached (e. g.; p. 254), and teaches addition and subtraction of free energy to meet accuracy constraints (pp. 254-258), thus anticipating claims 4,8, 12-l 3, 18, 29,41-43,46,49, and 51-56.

Applicant respectfully traverses the Examiner's rejection. Unlike the method of claim 1, Koehl does not teach generating a probability matrix for amino acids that represent a viable sequence space. Instead, Koehl teaches a method of determining rotamer conformations from a known amino acid sequence and a known backbone structure. This method is a solution to the inverse folding problem. Koehl provides a more explicit description of this problem and its converse, the reverse folding problem, at pages 250-251. These so-called "problems" are summarized in the table below:

"Problem"	Description	Input	Output	Disclosure in Koehl
Reverse folding	"consists in searching sequences that are compatible with a given fold." (p. 250)	structure	amino acid sequences	distinguished from Koehl's method (p. 250)
Inverse Folding	determining the folded structure of a protein from its sequence.	amino acid sequences	structure	Koehl's method is "a subset of the inverse protein folding problem." (p. 250)

As summarized above and on page 250 of Koehl, the reverse folding problem and the inverse folding problem differ.

Koehl describes her method, on page 250, as the "prediction of side chain conformations given a backbone conformation." The specific method taught by Koehl starts with the conformation of a protein backbone and an amino acid sequence. Koehl then predicts the rotamer conformation of amino acid side chains in the folded protein. For example, Koehl describes predicting the rotamer conformations for rhizopuspepsin using its known crystal structure and its known amino acid sequence at page 254-255:

> As an example, we give detailed information on the convergence of the method ALL for a medium size protein, rhizopuspepsin. It contains 325 residues, and its structure has been solved with X-ray crystallography to 1.8 Å

> resolution, with a R-factor of 14%. It co-ordinates were obtained from file 2apr . . . and side chains were energy minimized with CHARMM, as described above. The side-chain optimization was carried over 20 cycles.

As seen, Koehl uses the known backbone structure and the known amino acid sequence to predict the rotamer conformation of individual amino acids in the rhizopuspepsin sequence. Koehl does not determine which other amino acids might be compatible with the rhizopuspepsin backbone structure or any other structure.

Thus, Koehl does not teach or suggest generating a probability matrix for amino acids that represent a viable sequence space as required by the method of claim 1.

With respect to claims 8 and 19, for the reasons discussed above, Koehl does not teach or suggest probability matrix that represents the viable sequence space for a protein backbone. Accordingly, Koehl cannot anticipate claims 8 and 19. With respect to claim 51, Koehl does not teach first and second probability matrices for amino acids at positions in a protein sequence.

Claim 64 includes applying a design procedure to generate a protein sequence or set of protein sequences. As elaborated above, Koehl does not generate a protein sequence, but rather identifies rotamers for a known protein sequence. Thus, Koehl cannot anticipate or make obvious the method of claim 64.

Claim 65 includes generating a matrix of amino acid probabilities that represents a viable sequence space. Since Koehl does not generate a matrix of amino acid probabilities, Koehl also does not anticipate or make obvious the method of claim 65.

Obviousness Rejections

The Examiner stated:

> **Claims 1,4-8, 12-14, 16, 18-22,24,27-29,41-47,49,51-56 and 64-65 are rejected under 35 USC. 103(a) as being unpatentable over KOEHL et al. (J. Molec. Biol. (1994) vol. 239, pp. 249-275)in view of KOEHL et al. (Current Opinion Struct. Bio. (1996) vol. 6, pp. 222-226).**
>
> **KOEHL (1994) teaches a computerized method of generating a global conformational (probability)matrix representing a protein structure, as set forth above. KOEHL does not teach a Monte Carlo algorithm to generate an ensemble of proteins. KOEHL (1996)teaches a mean field Monte Carlo procedure to generate a family (ensemble)of proteins, and teaches that this provides**

significant improvement in an SCMF method of modeling proteins (p. 224). It would have been obvious to one of ordinary skill in the art at the time of invention to have included the Monte Carlo generation of KOEHL (1996)in the method of KEOHL (1994)where the motivation would have been to improve the SCMF method of modeling proteins, as taught by KOEHL.

Claims 2-3,25-26,38-40,48,50, and 60-61 are rejected under 35 U. S. C. 103(a)as being unpatentable over KOEHL et al. (J. Molec. Biol. (1994) vol. 239, pp. 249-275) in view of KOEHL et al. (Current Opinion Struct. Bio. (1996)vol. 6, pp. 222-226) as applied to claims 1,4-8, 12-14, 16, 18-22,24,27-29,41-43,46-47,49,51-56 and 64-65 above, and further in view of DAHIYAT et al. (Protein Sci. (1996) vol. 5, pp. 895-903).

KOEHL and KOEHL et al. and make obvious a computerized method of generating a global conformational (probability) matrix representing a protein structure, as set forth above. Neither KOEHL teaches generation or selection of a protein or proteins generated/designed by the method. DAHIYAT teaches a method of designing proteins from a backbone and rotamer library using a Monte Carlo algorithm (p. 901)and teaches selection and synthesis of the peptide library designed (p. 902). DAHIYAT teaches that proteins may be selected for stability (p. 895: Abstract). It would have been obvious to one of ordinary skill in the art at the time of invention to have selected and synthesized peptides, as taught by DAHIYAT which were generated in the method of KOEHL and KOEHL, where the motivation would have been to compare predicted to actual activity and stability of the peptides, as taught by DAHIYAT (abstract and p. 902). [emphasis added]

The Applicant understands the underscored language above to incorporate by reference the Examiner's rejection under § 102 in view of Koehl (1994). The Applicant has traversed this rejection above.

The additional references appear to be relied upon merely to reject certain dependent claims. Since the Examiner is not asserting that Koehl (1996) or Dahiyat teaches elements absent in Koehl (1994), the combination of Koehl (1994) and Koehl (1996) and the combination of Koehl (1994) and Koehl (1996) and Dahiyat cannot render the present claims obvious.

The Applicant takes no position at this time as to whether the other requirements for a prima facie obviousness rejection are met.

The Applicant respectfully submits that all claims are in condition for allowance, which action is expeditiously requested. The Applicant does not concede any positions of the Examiner that are not expressly addressed above, nor does the Applicant concede that there are not other good reasons for patentability of the presented claims or other claims. All amendments and

cancellations are made without prejudice and disclaimer and may be made for reasons not explicitly stated or for reasons in addition to ones stated.

Enclosed is a Petition for Extension of Time and a cheque for the required fee. Please apply any other charges, including charges for excess claims, to deposit account 06-1050, referencing attorney docket number 16380-002001.

Respectfully submitted,

Date: 24 Nov. 2004

Ramon K. Tabtiang
Reg. No. 55,658

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

70051453.doc